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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/367,859 | 09/02/1999 | JAMES SAMSOONDAR | 5352-051 | 4860 |

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| EXAMINER | |
|---|---|
| SODERQUIST, ARLEN | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1743 | |

DATE MAILED: 05/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/367,859 | SAMSOONDAR, JAMES | |
| | Examiner | Art Unit | |
| | Arlen Soderquist | 1743 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *13 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *8,10-12,23,24,27 and 29-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,10-12,23,24,27 and 29-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 13, 2004 has been entered.

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

3. Claims 8, 10-12, 23-24, 27 and 29-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davis in view of Sagusa, Gimpel, Simon and Christenson, Leissing or Mullins. In the patent Davis teaches a method of detecting hemolysis in a whole-blood sample, a method of determining an elevation in the potassium ion concentration of a whole-blood sample, an apparatus for detecting hemolysis and/or determining an elevation in the potassium ion concentration in a fluid sample, an apparatus for detecting hemolysis and/or determining an elevation in the potassium ion concentration in a whole-blood sample, and a single-use cartridge containing a plurality of microfabricated biosensors which further contains a hemolysis detection unit. Thus Davis separately detects the presence of hemoglobin in the blood sample consistent with the prior art as taught in column2, lines 46-52. Columns 2-3 of the application teach the interference from hemoglobin caused through hemolysis of red blood cells through both an increase in the concentration of other components found in the red blood cells or through colorimetric interference with chromogenic reagents. In particular the above noted column 2,

lines 46-52 teaches the prior method of checking the color of the plasma sample for the red coloration associated with the presence of hemolysis. Column 3, lines 12-18 list several analytes which can be affected through the presence of hemolysis including potassium, lactate dehydrogenase, cholesterol, prostatic phosphatase, aspartate aminotransferase, and alanine aminotransferase, aldolase, total acid phosphatase, isocitrate hydrogenase, magnesium and phosphate. Columns 6-8 teach how the presence of hemoglobin is detected with column 8 lines, 10-36 being particularly relevant to the instant claims. This section of column 8 teaches the use of a reflectance meter, the use of a direct measurement (no chromogenic reagent is used) and forming a calibration graph to determine the concentration of hemoglobin present. Columns 8-9 teach how the measurement of the hemoglobin concentration is used to correct the analyte measurement. Of particular interest is column 9, lines 44-56 teaching the relationships between hemolyzed red blood cells, the concentration of Hb, and the elevation of blood analytes such as potassium ion concentration. The relationship for potassium is taught as a linearly dependent relationship. As a result, those of ordinary skill in the art will be able to pre-select a value of hemolysis which corresponds to both a known concentration of Hb in plasma and the corresponding color thereof, which in turn correlates to a pre-selected elevation in the potassium ion concentration. Davis does not teach interference by blood substitutes or other components of the blood, using derivative spectroscopy in the correction equation or detection of pseudohemolysis.

In the patent Sagusa teaches a colorimetric method for samples including interfering chromogens from the presence of chyle, hemolysis and icterus. Column 3 discusses how these things interfere with the analysis of the analytes. Color former is added to blood serum sample color it, and measurements for specific components are determined based on the light absorbance caused by coloring. For one sample, a differential light absorbance between two wavelengths at each of long wavelength region, middle wavelength region and short wavelength region within a visible wavelength band is determined. The degree of chyle is determined from the measurements for the long wavelength region, the degree of hemolysis is determined from the measurements for the middle wavelength region, and the degree of icterus is determined from the measurements for the short wavelength region. The measurements for the specific components are then corrected by the degree of chyle, degree of hemolysis and degree of icterus to obtain

highly correct measurements. Column 4 shows some example wavelengths and columns 4-5 show how the degree of chyle, hemolysis and icterus are obtained and used to correct the analyte concentration. In this discussion equation (4) is particularly important because it shows that the relationship between each of the degree of chyle, hemolysis and icterus and the respective analytes are linear depending only on a constant and the concentration representative of the degree of chyle, hemolysis and icterus.

In the abstract Christenson discusses hemoglobin based blood substitutes and their interference with routine chemical tests.

In the abstract Leissing discusses modification of clinical chemistry methods to overcome interferences from diaspirin crosslinked hemoglobin (DCLHb).

In the paper Mullins discusses effects of Fluosol-DA (artificial blood) on clinical chemistry tests and instruments. Artificial blood must be added to the list of therapeutic agents that produce interference with diagnostic laboratory tests. Fluosol-DA (Alpha Therapeutic Corp., Los Angeles, CA), a stable 20% emulsion of perfluorocarbons in aqueous medium, is being evaluated in clinical trials as a blood substitute in the United States. They investigated its effects in blood and serum samples on test results and instruments in the clinical chemistry laboratory. The 20% emulsion was added to blood or serum specimens in amounts corresponding to the replacement of in-vivo plasma volumes of 10-50%, concentrations that would be expected in blood samples obtained from patients who have received Fluosol. Observed interferences mimicked those caused by high triglyceride concentrations in serum specimens: interference with chemical reactions and generation of spurious absorbance readings because of turbidity. These types of errors are often additive, and the cumulative effect may cause either erroneously high or low values for the analytes concerned. Because Fluosol may be used widely, although infrequently, for patients refusing blood transfusions on religious grounds and for patients with rare antibodies to red blood cells who require transfusion, laboratories analyzing specimens containing Fluosol should be aware of the potential errors.

In the paper Gimpel teaches a reference interval for the bilirubin excess in cerebrospinal fluid by derivative spectrophotometry. The value of the bilirubin excess can be a useful aid for recognizing blood from hemorrhage in cerebrospinal fluid. One of the parameters needed for the calculation of the bilirubin excess is the total bilirubin concentration in cerebrospinal fluid. A

method for measuring total bilirubin in cerebrospinal fluid is presented, based on diazotization of bilirubin according to Jendrassik-Grof, combined with multiwavelength first-derivative spectrophotometry. This bilirubin assay allows determination of total bilirubin concentrations as low as 0.045 μmol/L. This method also enables a correlation for oxyHb interference. The value of the bilirubin excess was calculated for patients not showing any neurological disorder. A reference interval of 0.07 ± 0.06 μmol/L was calculated for the bilirubin excess. Particularly relevant to the instant claims is the calculations and equations shown in the right column of page 218.

In the paper Simon discusses a "pseudo-hemolytic" transfusion reaction caused by intravenous iron-dextran therapy. Intravenous iron-dextran therapy can cause a red-brown discoloration of the plasma, simulating a hemolytic transfusion reaction. A rapid and simple test to differentiate between true hemolysis and plasma discoloration due to circulating iron-dextran complexes is described.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to include substances such as blood substitutes recognized by Christenson, Leissing or Mullins as interfering substances and other known interferents such as those taught by Sagusa into the Davis correction method because of the recognized possibility for interference with clinical chemistry tests and the projected use of these substances in humans. It would have been obvious to one of ordinary skill in the art at the time the invention was made to use different wavelengths as taught in the Sagusa method to differentiate between true hemolysis and plasma discoloration due to circulating colored substances as taught by Simon and Sagusa in the Davis method because of the ability to select wavelengths that will allow the effects of one chromogen to be removed from another chromogen as taught by Sagusa and the need to differentiate between true hemolysis and plasma discoloration due to circulating substances as taught by Simon. It would have been obvious to one of ordinary skill in the art at the time the invention was made to use a derivative spectroscopic method as shown by Gimpel for correction in the Davis method because of the ability to differentiate between interfering substances such as the hemoglobin and bilirubin of Gimpel. Determination of specific wavelengths would be a results

effective variable which has been held to be within the skill of the routineer in the art by the Courts (see *In re Boesch*, 205 USPQ 215 (CCPA 1980)).

4. Applicant's arguments filed February 13, 2004 have been fully considered but they are not persuasive. The Davis reference clearly deals with correction of analyses in the presence of an interfering substance such as hemoglobin from hemolysis of a blood sample and it separates the detection of the interfering substance from the detection of the analyte. Davis also clearly teaches the detection of the hemoglobin from hemolysis in the absence of a chromogenic reagent (column 8, lines 18-36). Relative to claim 8, the relationship in Davis between the hemoglobin concentration is linear. This same relationship exists in Sagusa between each of the interferents and the analyte being measured. Thus the use of a linear relationship would have been expected for the relationship with at least the interferents taught by Sagusa particularly in view of the fact that the interferent of Davis is one of those taught in Sagusa. Relative to claims 24 and 31, the claims do not explicitly require a classification or determination step and examiner is treating them as the detection of hemoglobin or a blood substitute constitutes the determination. The Davis reference recognizes that the presence of an interferent can interfere in two ways: increasing the concentration of a measured component from is release from the red blood cells through hemolysis and through interfering with the color formed in the analysis. The Sagusa reference shows that one of skill in the art also recognizes that interferences can interfere by overlapping the spectrum used to measure the analyte. Thus when the Christenson, Leissing or Mullins references teach that blood substitutes also interfere with the analysis of analytes, it would have been obvious to include them into the process for correcting the concentration of known interferents to overcome the known affects of an interfering compound as shown by both Davis and Sagusa. The presence of substances in the blood (blood substitutes) that would also interfere with an analysis in a manner similar to hemolysis is shown by the secondary references as well as means to remove the influence of the interfering compounds. Thus it would have been obvious to modify the teachings of Davis to include the possibility of pseudohemolysis due to its recognized presence and effects on the analysis of other components of a blood sample. Since the references are dealing with interfering substances in an analysis they are properly combinable. The Courts have recognized that a secondary reference does not need to be physically combinable with the primary reference to render the invention under review obvious.

Along these lines applicant is directed to *In re* Sneed 218 USPQ 385, 389 (Fed. Cir. 1983) and *In re* Keller 208 USPQ 871, 880 (CCPA 1981) .

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arlen Soderquist whose current telephone number is (571) 272-1265 as a result of the examiner moving to the new USPTO location. The examiner's schedule is variable between the hours of about 5:30 AM to about 5:00 PM on Monday through Thursday and alternate Fridays.

A general phone number for the organization to which this application is assigned is (571) 272-1700. The fax phone number to file official papers for this application or proceeding is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Arlen Soderquist

May 12, 2004

ARLEN SODERQUIST
PRIMARY EXAMINER